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ALEXANDRIA, VIRGINIA 22314-2700
703 837-9600

REMARKS

The Office Action of October 29, 2003 has been carefully considered.

In the previous amendment filed on July 23, 2003, new claims 31 and 32 were added to the application. The Office Action mailed on October 21, 2003 does contain any acknowledgment that these claims were added to the application, nor any indication that these claims were examined. Applicants therefore request that claims 31 and 32 be entered into the application.

As the application is currently under final rejection, the following amendments have been made to the claims in order to reduce the issues upon appeal, should appeal be necessary:

Claims 18 and 19 have been amended to delete all references to "conjugated equine estrogens," and claims 5, 9, 23, 27 and 32 which recited conjugated equine estrogens have been canceled. Consequently, the rejection under 35 USC 112, 1st paragraph has been rendered moot.

In addition, claims 6, 22 and 24 were considered duplicative of other claims, and have been canceled.

Claims 3, 4, 7, 13, 26, 30 and 31 have been amended to clarify the subject matter of those claims.

Claim 18 has been amended to recite a method of "correcting" as opposed to "preventing" estrogen deficiencies.

Entry of the above amendments into the application is requested.

While not specified in the Office Action, the claims apparently stand rejected under 35 USC 103 over Plunkett et al and Blanc et al, for the reasons set forth in the Office Action of February 24, 2003.

Plunkett et al discloses a method for treatment of menopausal disorders comprising continuous administration for

progestogen in combination with estrogen, where the estrogen in the form of estradiol can be administered continuously or intermittently. While estradiols and their esters are disclosed, the only examples are directed to cyclic or intermittent administration of estrogens and nomegestrol acetate is not disclosed at all.

The Blanc et al reference discloses continuous hormone replacement therapy for menopause comprising an oral dose of 2.5 mg/day nomegestrol acetate, and either percutaneous 17B-estradiol gel (1.5 mg/day), transdermal 17β-estradiol patch (50 μm/d) or oral estradiol valerate (2 mg/day).

According to the results discussed on pages 905-906, the amenorrhea rate (cycles with no bleeding) was 60% when oral nomegestrol acetate was combined with oral estradiol valerate, as compared to 78% when oral nomegestrol acetate was combined with *percutaneous* estradiol. There is no suggestion whatever in Blanc et al to lower the dose of nomegestrol acetate with a view towards correcting estrogen deficiencies or preventing osteoporosis, and, moreover, Applicants submit that one of ordinary skill in the art would not select the regimen where both the nomegestrol acetate and the estrogen are administered orally.

In fact, Blanc et al teaches that the rate of amenorrhea achieved with continuous combined HRT for menopause is an important factor in patient compliance (page 909, left column). Since according to Blanc et al the rate of amenorrhea is higher when nomegestrol acetate is combined with *percutaneous* estradiol, those of ordinary skill in the art seeking to improve the rate of amenorrhea and hence patient compliance would have been deterred from using an *oral* estrogen in combination with an oral nomegestrol acetate.

Moreover, Table 2 on page 24 of the present specification

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shows the results of biopsies of the endometrium for women treated with a combination of the invention. A comparison is made between the combination containing 2.5 mg of nomegestrol acetate (i.e. the dose disclosed in Blanc et al) and combinations containing lower doses of nomegestrol acetate as presently claimed. It can be seen from the results that the number of atrophic endometria significantly increased at the nomegestrol acetate doses of 1.25 mg (a 25% increase) and 0.625 mg (a 138% increase) as compared with the dose of 2.5 mg taught by Blanc et al.

This means that the endometrium is better protected utilizing the dose of the invention, because when the endometrium is atrophic, then no hyperplasia (excessive growth of tissue) occurs.

At the same time, the low dosage nomegestrol acetate which is presently claimed is insufficient to induce secretory transformation of the endometrium since, as can be seen from Table 2 of the present specification, the number of secretory endometria significantly decreases with the dose.

Accordingly, it is surprising and unexpected that at doses which are insufficient to introduce a secretory transformation of the endometrium, nomegestrol acetate, when administered with an estrogen, nevertheless exerts a protective effect on the endometrium by keeping it in an atrophic state. Such results cannot be deduced from the teaching of Plunkett et al, which does not disclose nomegestrol acetate at all, or Blanc et al, which utilizes a higher dose of nomegestrol acetate.

A question has been raised regarding the presentation of the declaration with the prior amendment. Applicants note that the declaration was presented in parent application Serial No. 09/284,147 which was also directed to

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administration of combinations of nomegestrol acetate and estrogens. The purpose of submission of the declaration in the present application was to point out clearly and unambiguously that nomegestrol acetate has different properties from other progestogens. This is relevant because the Plunkett et al reference, cited both in 09/284,147 and in the present application, fails to disclose nomegestrol acetate and its properties. Thus, the submission of this declaration provides additional evidence that one of ordinary skill in the art could not make a simple substitution of nomegestrol acetate for the progestogens disclosed by Plunkett et al, and predict the results of such a combination based upon the results of Plunkett et al.

Withdrawal of the rejections of record over Plunkett et al and Blanc et al is respectfully requested.

In view of the foregoing amendments and remarks, Applicants submit that the present application is now in condition for allowance. An early allowance of the application with amended claims is earnestly solicited.

Respectfully submitted,

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